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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/395,409	09/14/1999	CHARLES CANTOR	SEQ-1002-CT	6005

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GRANT ANDERSON LLP
C/O PORTFOLIOIP
PO BOX 52050
MINNEAPOLIS, MN 55402

EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/395,409	CANTOR ET AL.	
	Examiner	Art Unit	
	HEATHER G. CALAMITA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54,58-76,88-124,127-143 and 145-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54,58-76,88-124,127-143 and 145-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 19, 2008, has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 1-54, 58-76, 88-124, 127-143 and 145-147 are currently pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11, 31-34, 95, 96, 101 and 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11, 31-34, 95, 96, 101 and 102 all ultimately depend from claim 1 and claim 1 recites "consisting of" language. It is unclear how a method consisting of elements can further comprise additional elements. The language of "consisting of" requires that only the recited elements be present, therefore depending claims reciting "further comprising" language is indefinite.

Claims 1-54, 58-76, 88-123, 128, 145 and 146 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between

the steps. See MPEP § 2172.01. The omitted steps are: In claim 1, there should be for example, a step of dissociation of the hybridized nucleic acids. Additionally, how do you determine the molecular weights of the hybridized nucleic acids.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-54, 58-76, 88-123, 128, 145 and 146 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of sequencing a target nucleic acid molecule. The invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims consist of the steps of determining the sequence of a nucleic acid molecule by fragmenting the target nucleic acid molecule hybridizing the fragments to an array of probes and determining the molecular weights of the hybridized nucleic acids to identify the probes and then based on the identity of the probes determine the sequence of the target nucleic acid.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large as it is highly unpredictable how one will identify the probe from just determining the molecular weight of the probe. The identity of the probe cannot be determined from molecular weight alone as recited in instant claim 1. The molecular weight of the probe can be determined and the number of As, Ts, Cs and Gs can be known, however the order of these bases remains unknown. A skilled artisan will not be able to determine the identity of the probe and therefore cannot determine the sequence of the target molecule. If multiple hybridized sequences exist on an array and the fragments hybridized are of varying lengths then it is impossible to identify the probes and subsequently the sequence of the target without prior knowledge of each of the probe sequences. Here determining the molecular weight of the probe will not allow identification of the probe as claimed. Without identification of the probe then the sequence of the target cannot be determined. The claim as written does not require a known standard for comparison. The claim as written recites consisting of language and fails to recite all of the necessary elements needed to execute the method. Köster (WO 94/16101 07/21/1994) teaches determining the molecular weight of individual Sanger fragments and compares the mass difference measured between the nested fragments with the known masses of each of the chain terminating nucleotides which allows the sequence of each fragment to be determined. Here Köster recognizes the necessity of having a known standard.

The unpredictability of the art and the state of the prior art

The art is predictable with respect to sequencing and with respect to mass spectrometry.

However, it is highly unpredictable how one of skill in the art will identify the probe from just determining the molecular weight of the probe. The identity of the probe cannot be determined from molecular weight alone. The molecular weight of the probe can be determined and the number of As, Ts, Cs and Gs can be known, however the order of these bases remains unknown. A skilled artisan will not be able to determine the identity of the probe and therefore cannot determine the sequence of the target molecule. Additionally, as discussed above it is almost impossible to accurately order the bases of the multiple probes as a way to identify them. It can be determined the number of As, Ts, Cs and Gs present within each of the multiple probes, however it is not possible to then accurately order these bases as a means to identify the probes. As recited in instant claim 1, after the molecular weights of the probes are determined they are subsequently identified and then based on the identified probes the sequence of the target nucleic acid is determined. The claim as written recites consisting of language and fails to recite all of the necessary elements needed to execute the method. It is not possible to determine the sequence of the target nucleic acid because it is not possible to identify the probes as currently claimed.

Working Examples

The specification has no working examples that are commensurate in scope with the instant claims.

Guidance in the Specification.

The specification provides no specific or substantial guidance for using the molecular weight of a probe as a means to identify the probe and subsequently determine the sequence of a target nucleic acid. There is no guidance as to how to identify the probe based on molecular weight alone. While the molecular weight of the probe can be determined and the number of As, Ts, Cs and Gs can be known, there is no guidance as to how to order these bases.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the lack of working examples balanced only against the high skill level in the art, it is the position of the Office that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 124, 127 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Köster (WO 94/16101 07/21/1994) and Cantor (USPN 5,503,980, 04/02/1996) in view of .

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37

CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

With regard to claim 124, Köster teaches an array of nucleic acid probes wherein the array is attached to a solid support comprising a matrix chemical that facilitates volatilization of nucleic acids for molecular weight determination (see p. 16 lines 13-24 and line 31).

The array comprises a nucleic acid probe having at least one mass modifying functionality that increases the discrimination between the nucleic acid probe with the mass modifying functionality and a another nucleic acid molecule when detected by mass spectrometry (see p. 15 lines 9-12)

With regard to claim 127, Köster teaches a system, comprising: a mass spectrometer; a computer; (see p. 11 lines 28-30, and p. 20 lines 33-38).

With regard to claim 129, Köster teaches the mass-modifying functionality is coupled to a heterocyclic base, a sugar moiety or a phosphate group (see p. 15 lines 9-12).

With regard to claim 130, Köster teaches the mass-modifying functionality is selected from the group consisting of F, CI, Br, I, SiR_3, $Si(CH_3)_3$, $Si(CH_3)_2(C_2H_5)$, $Si(CH_3)(C_2H_5)_3$, $(CH_2)_nCH_3$, $(CH_2)_nNR_2$, CH_2CONR_2, $(CH_2)_nOH$, CH_2F, CHF_2, and CF_3; wherein n is an integer; and wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylaled polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol (see Figs 9 and 10)

With regard to claim 131, Köster teaches the mass-modifying functionality is -Na or -XR, wherein X is selected from the group consisting of -0-, -NH-, -NR-, -S-, $-OCO(CH_2)_nCOO-$, -

$NHCO(CH_2)_nCOO$-, $-OSO_2O$-, $-OCO(CH_2)_n$-, -NHC(O)-, and -C(O)NH-, and n is an integer from 1 to 20; and wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylated polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol (see Figs 9 & 10).

With regard 132, Köster teaches the mass-modifying functionality is a thiol moiety (see p. 15 lines 7-10).

With regard to claim 136, Köster teaches the solid support is selected from the group consisting of plates, beads, microbeads, whiskers, combs, hybridization chips, membranes, single crystals, ceramics, and self-assembling monolayers (see p. 16 lines 13-16).

With regard to claim 137, Köster teaches the probes are conjugated with biotin or a biotin derivative and wherein the solid support is conjugated with avidin, streptavidin or a derivative thereof (see p. 15 line 17).

With regard to claim 138, Köster teaches each probe is attached to the solid support by a bond selected from the group consisting of a covalent bond, an electrostatic bond, a hydrogen bond, a cleavable bond, a pholocleavable bond, a disulfide bond, a peptide bond, a diester bond, a selectively releasable bond and combinations thereof (see p. 15 lines 14-24).

With regard to claim 143, Köster teaches the probes comprise DNA, RNA, PNA or combinations thereof (see p. 14 lines 35-37).

With regard to claim 147, Köster teaches the matrix chemical is 3-hydroxypicolinic acid, sinapinic acid or dihydroxybenzoic acid (see p. 38 lines 24-25).

Köster does not teach the probe comprises a single-stranded variable region.

Köster does not teach the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

Köster does not teach probes that comprise a double stranded portion and a single stranded portion. Köster does not teach the probes are about 10 to about 1,000 nucleotides in length. Köster does not teach the variable region is about 4-20 nucleotides in length. Köster does not teach the single stranded region is about 4-20 nucleotides in length. Köster does not teach the fragments of nucleic acids comprise greater than about 104 different members and each member is between about 10 to about 1,000 nucleotides in length. Köster does not teach the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

Cantor teaches an array and a probe with a single stranded variable region and the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (see col. 12 lines 6-17).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of probes with sequence diversity in the variable regions to hybridize all of the target sequence with nearly complete discrimination as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster in order to improve the analysis of the nucleic acids sequences. Cantor states, "Only the overhangs vary, and in principle an array of 4^n probes is needed to represent all 4^n possible overhangs of length n. The advantage of such an array is that it provides enhanced sequence stringency in detecting the 5' terminal nucleotide of the target DNA because of base stacking between the preformed DNA duplex and the newly formed duplex (see col. 12 lines 10-16). It would have been prima facie obvious to apply the method of generating probes with sequence diversity in the variable regions to hybridize all of the target sequence with nearly complete discrimination as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster to achieve the expected advantage of enhanced sequence stringency in detecting the 5' terminal nucleotide of the target DNA and therefore enable more accurate sequencing of the target DNA.

Additonally, Cantor teaches probes with a double stranded portion and a single stranded portion, the probes are about 10 to about 1,000 nucleotides in length, the variable region is about 4-20 nucleotides in length, the single stranded region is about 4-20 nucleotides in length (see whole document especially col. 3 lines 32-36, see col. 5 lines 53-59, col. 7 lines 65-67 and col. 8 lines 1-7). Cantor teaches the fragments of nucleic acids comprise greater than about 104 different members and each member is between about 10 to about 1,000 nucleotides in length and the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (see col. 6 lines 1-6).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the probes as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster in order to improve nucleic acid sequencing. Cantor states, "This invention is directed to methods for sequencing nucleic acids by positional hybridization, to procedures combining these methods with more conventional sequencing techniques, to the creation of probes useful for nucleic acid sequencing by positional hybridization, to diagnostic aids useful for screening biological samples for nucleic acid variations, and to methods for using these diagnostic aids" (col. 1 lines 10-16). It would have been prima facie obvious to apply the probes as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster to achieve the expected advantage of an improved sequencing method conferring the advantage of accurate high throughput analysis.

6. Claims 139-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Köster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980, 04/02/1996) and in further view of Sanghvi et al. (USPN 6,214,551 04/10/2001).

The teachings and suggestions of Köster and Cantor are described previously.

Köster and Cantor do not teach or suggest the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof including 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid.

Sanghvi et al. teach the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof (see example 81, col. 58 lines 3-32). Although Sanghvi et al. do not teach the derivative 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid in particular, Sanghvi et al. disclose equivalent compounds and derivatives used for the same purpose (Example 81).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the selectively releasable bond of 4,4'-dimethoxytrityl or a derivative thereof as taught by Sanghvi with the method for sequencing nucleic acid by mass spectrometry as taught by Köster and Cantor in order to have a selectively releasable bond. Sanghvi et al. state, "This invention is also directed to methods for the selective binding of RNA for research and diagnostic purposes. Such selective, strong binding is accomplished by interacting such RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize more strongly and with greater fidelity than known oligonucleotides or oligonucleotide analogs" (col. 31 lines 19-25). It would have been prima facie obvious to apply Sanghvi's selectively releasable bond of 4,4'-dimethoxytrityl or a derivative thereof with Köster's method for sequencing nucleic acid by mass spectrometry to achieve the expected advantage of an invention directed to methods for the selective binding of RNA for research and diagnostic purposes where such selective, strong binding is accomplished by interacting RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize with greater strength and fidelity than known oligonucleotides or oligonucleotide analogs.

Response to Arguments

7. Applicants' arguments with respect to the 1-54, 58-76, 88-123, 128, 145 and 146 have been considered but are moot in view of the new ground(s) of rejection.

With respect to claims 124 and dependent claims 127, 129-143 and 147, Applicants argue Köster does not teach an array of nucleic acid probes where each probe includes a single-stranded portion and a constant double-stranded portion or an array of probes having sufficient sequence diversity in the variable regions to hybridize to all of the target nucleic acid molecules with complete or nearly complete discrimination or probes that are about 10 to about 1000 nucleotides in length or probes that include a variable region of about 4-20 nucleotides in length. This argument is not persuasive because Köster is not relied on for these teachings Cantor is relied on for these teaching and as outlined in the rejection above teaches these features. With respect to the argument regarding mass modification, this argument is not persuasive for reasons already made of record on p. 15 of the final office action mailed February 20, 2008.

Summary

8. No claims were allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Heather G. Calamita/
Examiner, Art Unit 1637